DETAILED ACTION

Applicant's response without traverse, received 1/28/08, to the election requirement, mailed 12/27/07, electing 3-(2-butynyl)-5-methyl-2-(piperazin-1-yl)-3,5-dihydroimidazo[4,5-d]pyridazin-4-one (i.e. compound 2 in claim 16) as the dipeptidyl peptidase IV inhibitor species, metformin as the biguanide species, and diabetes as the disease species, is acknowledged.

Applicant's statement that claims 5-9, 11-16, and 24-26 read on the elected species is acknowledged and made of record

Applicant's preliminary claim amendment filed 1/28/08 is also acknowledged.

Status of the Claims

Claims 5-16, 24-26, 29, and 33 are currently pending in this application.

Claims 10, 29 and 33 are withdrawn for being directed to non-elected subject matter.

Claims 5-9, 11-16, 24-26 are presented for examination.

Restriction/Election

The election requirement is made final.

Foreign Priority

Receipt of the Non-English certified copies of the foreign priority application documents are acknowledged. It is noted that the effective filing date of the instant application is considered to be September 22, 2003 (i.e. the filing date of PCT/JP03/12075) for prior art purposes in the absence of a certified copy of the English translation.

Objection to the Claims

Claim 5 is objected to for reciting the terms "<Substituent group B>" and "however."

Applicant is required to correct the above deficiencies. It is suggested that these deficiencies may be overcome by a) substituting the term "<Substituent group B>" with the term "substituent group B" and b) deleting the term "however."

Claim Rejections – 35 USC 112 – First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-9, 11-16, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for therapeutic compounds/compositions for use in the treatment of a disease associated with active circulating GLP-1 and/or GLP-2, does not reasonably provide enablement for preventive agents/compositions or therapeutic compounds/compositions for treating any and all diseases associated with active circulating GLP-1 and/or active circulating GLP-2. This is a scope of enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if its is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth in *In re Wands,* 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman* 230 USPQ 546 (BdApls 1986) at 547 the court cited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art.

The invention in general relates to a preventive or therapeutic pharmaceutical composition comprising a dipeptidyl peptidase IV inhibitor and a biguanide agent.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. It is noted that the chemical and medical arts are generally unpredictable, requiring each embodiment to be individually assessed for chemical, pharmacologic, pharmaceutical, and clinical efficacy. The more unpredictable an area, the more specific enablement is necessary in order to satisfy the statue. (see *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970)).

Arch et al. (US Patent 7,078,397) teach methods comprising co-administration of a dipeptidyl peptidase IV inhibitor and another antidiabetic agent or the sequential administration thereof (col. 2, lines 31-46). Arch et al. teach that suitable antidiabetic agents for use in combination with a dipeptidyl peptidase IV inhibitor, includes a biguanide such as metformin (col. 2, lines 47-52

Drucker (US Patent 6,051,557) teaches that GLP-2 and peptide analogs of GLP-2 can cause proliferation of the tissue in the upper gastrointestinal tract (col. 1, line 61 to col. 2, line 5). Drucker also teaches method of treating subjects with inflammatory conditions comprising administering a tGLP-2 analog (col. 2, lines 7-40).

Haffner et al. (US Patent 7,132,443) teach that dipeptidyl peptidase IV (DPP-IV) is believed to regulate multiple important physiologic peptides, including but not limited

to, GLP1, GIP, GRP, GLP2 (col. 1, line 18 to col. 2, line 50). Haffner et al. teach that GLP-1 enhances insulin secretion and decreases hepatic glucose production, gastric emptying time, and food intake (col. 2, lines 9-12). Haffner et al. teach that GLP-2 maintains the integrity of the intestinal mucosal epithelium via effects on gastric motility, nutrient absorption, cryptic cell proliferation and apoptosis, and intestinal permeability (col. 2, lines 12-15).

2. The breadth of the claims

The instant claims are relatively broad in scope. For example, claim 5 recites the term "dipetidyl peptidase IV inhibitor," which given its broadest reasonable possible interpretation, is construed to encompass drugs that inhibit GLP1 and GLP2, as well as other peptides as evidenced by the above referenced teaching of Haffner et al. (cols. 1-2). Claim 5 also recites the term "one or more substituents" which reasonably encompass any number of substituents as the term "more" does not have an upper limit. Besides, the term "one or more substituents" encompass known and unknown substituents because the instant specification fails to provide clear and precise definition of said term. Claim 25 recites the term "preventive … agent for a disease which is associated with active circulating GLP-1 and/or active circulating," which is very broad. For example, the term "preventive" given its broadest reasonable possible interpretation is construed to mean absolute absence of the targeted disease/condition or cure of said disease/condition (see Webster). The term "associated" is also very broad. Because the therapeutic effect of dipetidyl peptidase IV inhibitors would necessarily vary depending

upon the specific chemical compound, the level of predictably in practicing the claimed invention would be greatly diminished.

3. The amount of direction or guidance provided and the presence or absence of working examples

Based on the instant disclosure, the applicant at best has provided specific direction or guidance only for a general method of making and using the agents encompassed by the instant claims.

4. The quantity of experimentation necessary

In view of the uncertainty and unpredictability of the art as evidenced by the discussion of the prior art, it is reasonable to surmise that this level of uncertainty in the art would require one skilled in the art to conduct more than routine experimentation in order to practice the claimed invention commensurate with the scope of the claims.

For the reasons stated above, claims 5-9, 11-16, 24-26 are rejected under 35 USC 112, first paragraph, for lack of scope enablement because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims.

LACK OF WRITTEN DESCRIPTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH:

Claims 5-9, 11-16, 24-26 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses chemicals which meet the written description and

enablement provisions of 35 USC 112, first paragraph. However, claims 5-9, 11-16, and 24-26 are directed to encompass compounds with “one or more substituents” which only correspond in some undefined way to specifically instantly disclosed chemicals. None of the undisclosed compounds with “one or more substituents” meet the written description provision of 35 USC § 112, first paragraph, due to lacking chemical structural information for what they are and chemical structures are highly variant and encompass a myriad of possibilities. The specification provides insufficient written description to support the genus encompassed by the claim.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the above specifically disclosed chemical structures, the skilled artisan cannot envision the detailed chemical structure of the encompassed compounds, analogs, etc., regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The chemical structure itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmacentical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> ...To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.* , 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli* , 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using

> "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood* , 107 F.3d at 1572, 41 USPQ2d at 1966.

Therefore, only the disclosed chemically structurally defined chemicals, but not the full breadth of the claim(s) meet the written description provision of 35 USC § 112, first paragraph. The species specifically disclosed are not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC § 112 is severable from its enablement provision. (See page 1115.)

Claim rejections – 35 USC 112 – Second Paragraph

The following is a quotation of the second paragraph of 35 USC 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the term “and/or,” which renders the claimed subject matter unclear because the term "and" and the term "or" have materially different meanings. It is suggested that this rejection may be overcome by amending the claim to delete either the term "and" or the term “or” provided the amendment is supported by the specification as originally filed.

112, 1st scope

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-9, 11-16, and 24-26 are rejected under 103(a) as being unpatentable over Arch et al. (WO 01/97808 A1; equivalent to US Patent 7,078,397), and Yoshikawa et al. (US Patent Application Pub. No. 2004/0116328).

No patentable weight is being given to the intended use of the claimed pharmaceutical composition.

Arch et al. (US Patent 7,078,397) teach methods comprising co-administration of a dipeptidyl peptidase IV inhibitor and another antidiabetic agent or the sequential administration thereof (col. 2, lines 31-46). Arch et al. teach that suitable antidiabetic

agents for use in combination with a dipeptidyl peptidase IV inhibitor, includes a biguanide such as metformin (col. 2, lines 47-52). However, Arch et al. do not teach compositions comprising applicant's elected combination of 3-(2-butynyl)-5-methyl-2-(piperazin-1-yl)-3,5-dihydroimidazo[4,5-d]pyridazin-4-one and metformin.

Yoshikawa et al. (US Patent Application Pub. No. 2004/0116328) teach 3-(2-butynyl)-5-methyl-2-(piperazin-1-yl)-3,5-dihydroimidazo[4,5-d]pyridazin-4-one (i.e. applicant's elected dipeptidyl peptidase IV inhibitor species) as a therapeutic agent for treating diabetes mellitus (para. 0112—0113).

Above references in combination make clear that 3-(2-butynyl)-5-methyl-2-(piperazin-1-yl)-3,5-dihydroimidazo[4,5-d]pyridazin-4-one and metformin have been individually used for the treatment of diabetes and/or obesity. It is obvious to combine two compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)*.

Thus, someone of skill in the art at the time the instant invention was made would have found it obvious to create the instant claimed invention with reasonable predictability.

Relevant Art of Record

The below cited art made of record and relied upon is considered pertinent to applicant's invention.

Whitcomb et al. (6,011,049) teach a method of treating diabetes by administering to a subject in need of treatment a combination of a sulfonylurea antidiabetic agent and an antidiabetic glitazone, together with a biguanide antidiabetic agent such as metformin, or simply a glitazone together with a biguanide; clinical data are disclosed to establishing the unexpected biological benefits achievable with these combinations (col. 1, lines 17-49). Applicant's elected invention is directed to a composition comprising a dipeptidyl peptidase IV inhibitor, and metformin. Although Whitcomb et al. teach that diabetes mellitus is progressive in nature, and can often be controlled initially by diet alone, but generally requires treatment with drugs such as sulfonylureas and injections of exogenous insulin, Whitcomb et al. do not teach compositions comprising a dipeptidyl peptidase IV inhibitor and metformin (col. 1, lines 17-32).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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21 May 2008
Examiner /C.R./

/Brian-Yong S Kwon/
Primary Examiner, Art Unit 1614